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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,286	07/27/1999	ANUPAMA K. NADKARNI	CPI-099	6674

7590 04/04/2003

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	23

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/362,286	NADKARNI ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 43-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14, 43-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Formal Matters

Claims 1-14, 43-59 are pending and under consideration.

Response to Amendment

The rejection of claims 1, 5, 8, 10-11, 43 under 35 U.S.C. 102(b) as being anticipated by Navarro et al. (WO 92/18641) has been withdrawn based on the argument that Navarro et al. does not teach mutant receptors with a greater signal than wild-type receptors.

The rejection of claims 1-2, 4-5 and 11-12 under 35 U.S.C. 102(b) as being anticipated by Bergsman et al (WO 96/18651) has been withdrawn based on the argument that Bergsman et al. does not teach mutant receptors with a greater signal than wild-type receptors.

The rejection of claims 1, 5 and 11-13 under 35 U.S.C. 102(b) as being anticipated by Hinuma et al. (EP 0711830A2) has been withdrawn based on the argument that Hinuma et al. does not teach mutant receptors with a greater signal than wild-type receptors.

The rejection of claims 8, 13 and 43-59 under 35 USC § 112 second paragraph for recitation of the terms "IL-8" and "galanin" receptors has been withdrawn.

The rejection of claims 44-59 under 35 USC § 112 first paragraph has been withdrawn.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 43 stand rejected under 35 U.S.C 112, first paragraph, because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor, for reasons of record set forth in Paper No. 19, 6/12/2002. There is not adequate guidance as to the nature of the mutant mammalian G protein coupled receptor which Applicants claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim.

Applicant argues that the specification sets forth methods for making mutant G protein coupled receptors, and methods for screening for mutant GPCR's which have increased signaling. However, the unpredictability of the protein art is shown in Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Mikayama et al. (1993) which teaches that

the human glycosylation-inhibiting factor (GIF) protein differs from human migration inhibitory factor (MIF) by a single amino acid residue (page 10056, Figure 1). Yet, despite the fact that these proteins are 90% identical at the amino acid level, GIF is unable to carry out the function of MIF, and MIF does not exhibit GIF bioactivity (page 10059, second column, third paragraph). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

There is no guidance provided in the specification as to how one of ordinary skill in the art would generate a mutant GPCR polypeptide other than those exemplified in the specification. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims included in the instant rejection encompass any and all GPCR's with a mutation in an X1X2X3X4 motif and recite the functional limitation that the encoded protein can generate a signal greater than the signal generated by a wild-type protein.

Applicant argues that the Specification has provided working examples of mutant GPCR's with enhanced activity. The Specification has provided examples of IL8A and galanin receptors with enhanced activity. However, the claims encompass any and all GPCR's with a mutation, while the references cited have demonstrated that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited.

(2) the nature of the invention - The instant invention is a mutant protein. Applicant argues that given the common structural features of GPCR's, one of skill in the art could easily extend these teachings to other GPCR's. However, certain positions in the protein sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Applicant has not taught which sequences are critical to the enhancement of GPCR function for any and all GPCR's as are encompassed by the claims.

(3) the state of the prior art - The Mikayama and Voet references demonstrate that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function, while the Bowie reference teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of

predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. Additionally, the Gether reference is cited to further show the unpredictability of structure to function determinations in the GPCR superfamily. Gether teaches that GPCRs do not share any overall sequence homology. The only structural feature common to all GPCRs is the presence of seven transmembrane-spanning α-helical segments connected by alternating intracellular and extracellular loops, with the amino terminus located on the extracellular side and the carboxy terminus on the intracellular side (page 91, column 1, second paragraph). The three major subfamilies of GPCR's include the receptors related to the "light receptor" rhodopsin and the β 2 -adrenergic receptor (family A), the receptors related to the glucagon receptor (family B), and the receptors related to the metabotropic neurotransmitter receptors (family C) (page 91, column 1, second paragraph). The overall homology among all type A receptors is low and restricted to a number of highly conserved key residues The high degree of conservation among these key residues suggests that they have an essential role for either the structural or functional integrity of the receptors (page 91, column 1, third paragraph). Family B receptors include approximately 20 different receptors for a variety of peptide hormones and neuropeptides, such as vasoactive intestinal peptide (VIP), calcitonin, PTH, and glucagon (page 92, Fig. 1). Except for the disulfide bridge connecting the second (ECL 2) and third extracellular loops (ECL 3), family B receptors do not contain any of the structural features characterizing family A receptors (page 91, column 2, second paragraph). Family C receptors have, like family A and B receptors, two putative disulfide-forming cysteines in ECL 2 and ECL 3, respectively, but otherwise they do not share any conserved residues with family A and B receptors (page 92, Fig. 1 and page 91,

column 2, third paragraph). The Gether reference thus teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. The instant claims encompass any and all GPCR's with a mutation in an X1X2X3X4 motif and recite the functional limitation that the encoded protein can generate a signal greater than the signal generated by a wild-type protein, while the specification provides examples for IL-8A and galanin receptor mutants with enhanced activity.

Applicant argues that the previous references cited by the Examiner are out of date, and cites a reference by Burkhard Rost which stands for the proposition that secondary structure predictions are increasingly becoming the work horse for numerous methods aimed at predicting protein structure and function. However, enablement is determined at the time of filing. The cited reference is a 2001 reference while the instant application has an effective filing date in 1998. Additionally, the Rost reference teaches that while methods of predicting protein secondary structure, i.e. helix or strand structure, are improving, the field is missing a variety of approaches relating secondary structure predications explicitly to function (see page 214, column 2, second paragraph). Thus, according to the Rost reference, even as late as 2001, structure to function predications remain unpredictable.

(5) the level of predictability in the art - The Mikayama, Voet and Bowie references demonstrate the unpredictability of the protein art. The Gether reference teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known.

Applicant argues that the common physical characteristics of the GPCR's were well known to one of ordinary skill in the art at the time of filing, and the specification contains structural and functional information on the GPCR's. However, as demonstrated, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's function from mere sequence data are limited. Given the large and diverse nature of the GPCR superfamily, and the lack of conservation of residues or motifs across the families, one of skill in the art would need to make each and every possible mutant GPCR and test for enhanced function, since there is no direction provided in the specification as to which of the residues or motifs are critical for the enhanced activity, and whether this motif is conserved across the entire superfamily of GPCR's. Since detailed information regarding the structural and functional requirements of the proteins are lacking, it is unpredictable as to which variations meet the limitations of the claims for enhanced activity.

(6) the amount of direction provided by the inventor - Applicant has only taught a mutant IL-8A and mutant galanin receptor. Applicant argues that given the common structural features of GPCR's one of ordinary skill in the art can extend these teachings to any and all GPCR's. However, as set forth above, certain positions in the protein sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Applicant has not taught which sequences are critical to the enhancement of GPCR function for any and all GPCR's as are encompassed by the claims, and the superfamily of

GPCR's is very large with a diversity of structure, while critical residues or motifs are not conserved between the families.

(7) the existence of working examples - Working examples are provided only for a mutant IL-8A and mutant galanin receptor, not any other mutant receptor protein. Applicant argues that working examples are not required for all encompassed embodiments. While this is true, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. In the instant case there are a large number of mutant GPCR's which would meet the structural limitations of the claims, but one of skill in the art would need to make each and every possible mutant GPCR and test for enhanced function, since there is no direction provided in the specification as to which of the residues or motifs are critical for the enhanced activity, and whether this motif is conserved across the entire superfamily of GPCR's, while only a few examples are provided.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Applicant argues that the Bowie, Mikayama and Voet references do not establish the unpredictability of the protein art, in view of the Rost reference cited by Applicant. However, the Rost reference clearly sets forth that, even as late as 2001, structure to function predications remain unpredictable. Therefore, given the breadth of claims 1-14, 43 and

based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, the Mikayama et al. and Voet et al. references which demonstrates that the change of a single amino acid can radically alter protein function, and the Gether reference which teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known, and absent sufficient evidence to the contrary, a preponderance of the evidence demonstrates that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 1-14, 43 stand rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 19, 6/12/2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant argues that the specification teaches distinguishing structural features within the claimed genus, such as the mutations of the IL8A and galanin receptors. However, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only two species within the genus.

As set forth *supra*, the protein art is unpredictable based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, the Mikayama et al. and Voet et al. references which

demonstrates that the change of a single amino acid can radically alter protein function and the Gether reference which teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. Additionally, the Rost reference cited by Applicant demonstrates the unpredictability of structure to function predications as late at 2001. The claims included in the instant rejection encompass any and all GPCR's with a mutation in an X1X2X3X4 motif and recite the functional limitation that the encoded protein can generate a signal greater than the signal generated by a wild-type protein. Applicant has taught a mutant IL-8A and mutant galanin receptor with an enhanced activity. The specification has not set forth functional characteristics coupled with a known or disclosed correlation between structure and function. Because one of skill in the art could not be expected to predict the biological activity of the sequence variants encompassed by the claims, the written description requirement has not been met. The specification provides a written description only for mutant IL8A and galanin receptors with the mutations as set forth in claims 44 and 52.

Applicant further argues that the claimed genus is of the mutant GPCR's is defined by the structural features of the X1X2X3X4 motif as described in the specification, and commonly possessed by its members. The written description requirement for a claimed genus may be satisfied by sufficient description of a representative number of species by functional characteristics coupled with a known or disclosed correlation between structure and function structure. In the instant case, the Gether reference teaches the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. Applicant has not taught which

sequences are critical to the enhancement of GPCR function for any and all GPCR's, as are encompassed by the claims, and the superfamily of GPCR's is very large with a diversity of structure, while critical residues or motifs are not conserved between the families. Because one of skill in the art could not be expected to predict the biological activity of the sequence variants encompassed by the claims, the written description requirement has not been met. The specification provides a written description only for mutant IL8A and galanin receptors with the mutations as set forth in claims 44 and 52.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 43-59 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record set forth in Paper No. 19, 6/12/2002.

The term "proximal" in claim 1 is a relative term which renders the claim indefinite. The term "proximal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-14 and 43-59 are rejected insofar as they depend on the recitation of the term "proximal".

Applicant cites Webster's Dictionary to demonstrate that the term 'proximal" means "situated close to". However, the indefinite nature of the term "proximal" is demonstrated in claim 44, wherein the X1X2X3X4 motif is set forth as being "proximal" to the C-terminal end

(which is approximately at amino acid 355, see Figure 2), while the claim is drawn to a mutant IL-8A receptor wherein the mutation in the motif is at amino acid residue 73. This cannot be considered as "proximal" to the C-terminal end, and demonstrates that the term "proximal" is not being used in a manner consistent with the motif being situated near the C-terminal end. Therefore the metes and bounds of the claims cannot be determined.

Claim 53 is vague and indefinite in that it is drawn to an "amino acid motif". It appears to be meant to be drawn to a mutant galanin receptor of claim 52 comprising the mutant amino acid motif. Claims 54-59 are rejected insofar as they depend on the term "amino acid motif" in claim 53.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 22, 2003

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